gli inibitori del PCSK9:

quando usarli?

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CONGRESSO REGIONALE AMD - SID

Alleanza strategica nella gestione del paziente diabetico: attori a confronto
Roma, 5-6 maggio 2017

•Il dr. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle Aziende Farmaceutiche e/o Diagnostiche

•Astra Zeneca

•Boehringer Ingelheim

•Eli-Lilly

•MSD

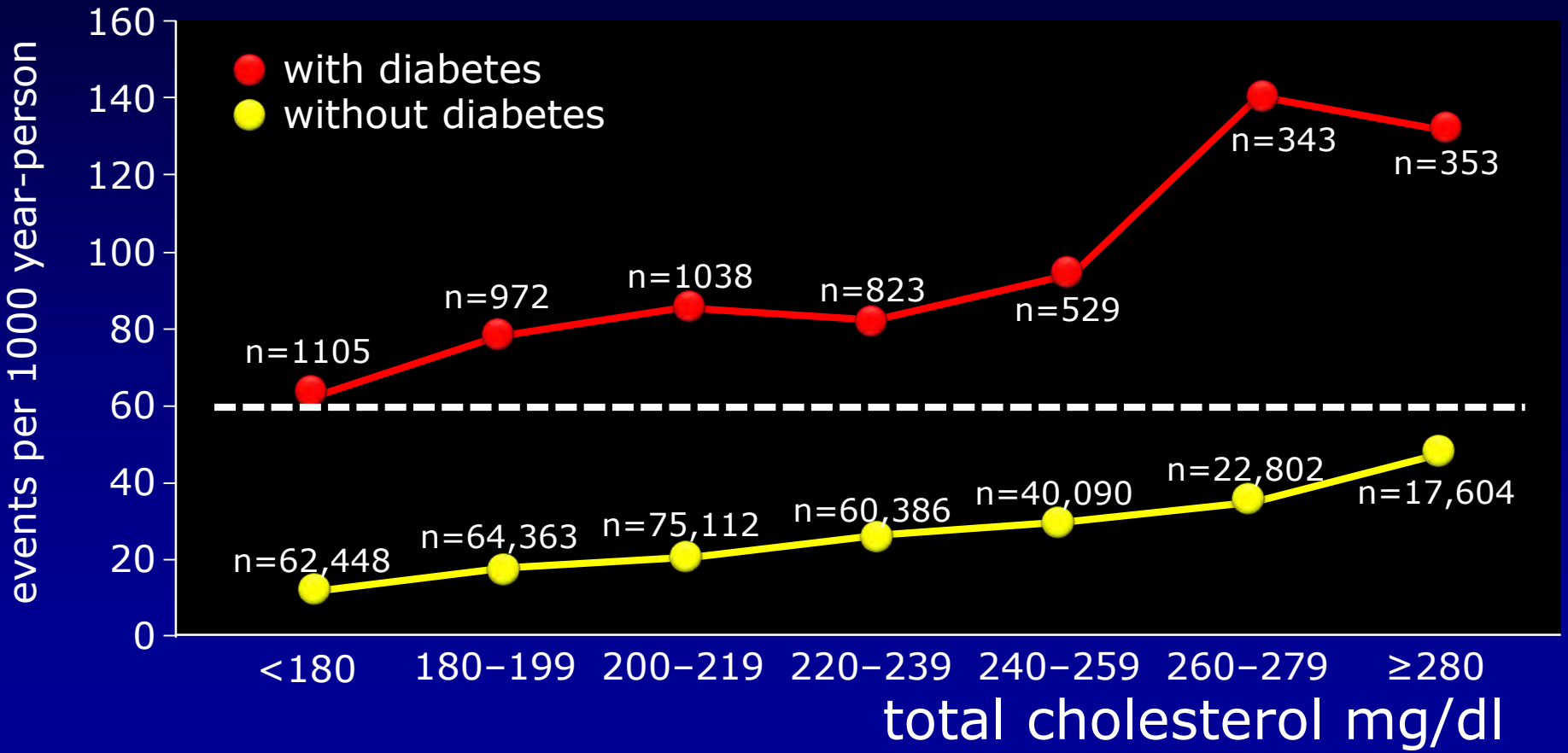
•Sanofi

•Takeda

MRFIT: Cardiovascular Mortality

patients with diabetes and low cholesterol have higher CV risk than patients with high cholesterol without diabetes

347,978 males followed for 12 years for CV mortality



MRFIT = Multiple Risk Factor Intervention Trial.

Stamler et al. Diabetes Care 16:434, 1993

2016 ESC/EAS Prevention Guidelines

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.

Recommendations[d e]	Class[a]	Level[b]
In patients at VERY HIGH CV risk, an LDL-C goal <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.[f]	I	B

NOTA 13

- 1. Principio della rimborsabilità è il valore target di **colesterolo LDL** da raggiungere.
- 2.a La presenza di **diabete di per sé** comporta la presenza di "alto rischio", pari a Malattia Coronarica (obiettivo terapeutico LDL < 100 mg/dl); in questo caso deve essere prescritta una **statina di I livello** (atorva, simva, prava, fluva o lova);
- 2.b se dimostrata inadeguata deve essere prescritta una **statina di II livello** (rosu o associazione con ezetimibe);

NOTA 13

- 3. a La presenza di **diabete insieme con con uno o più fattori di rischio CV e/o markers di danno d'organo** comporta la presenza di "rischio molto elevato" (**obiettivo terapeutico LDL < 70 mg/dl**);
- 3.b in caso di intolleranza o inefficacia può essere prescritta **direttamente rosuva**;
- 3.c se tali statine non sono tollerate o efficaci **è possibile associare ezetimibe** (II livello).

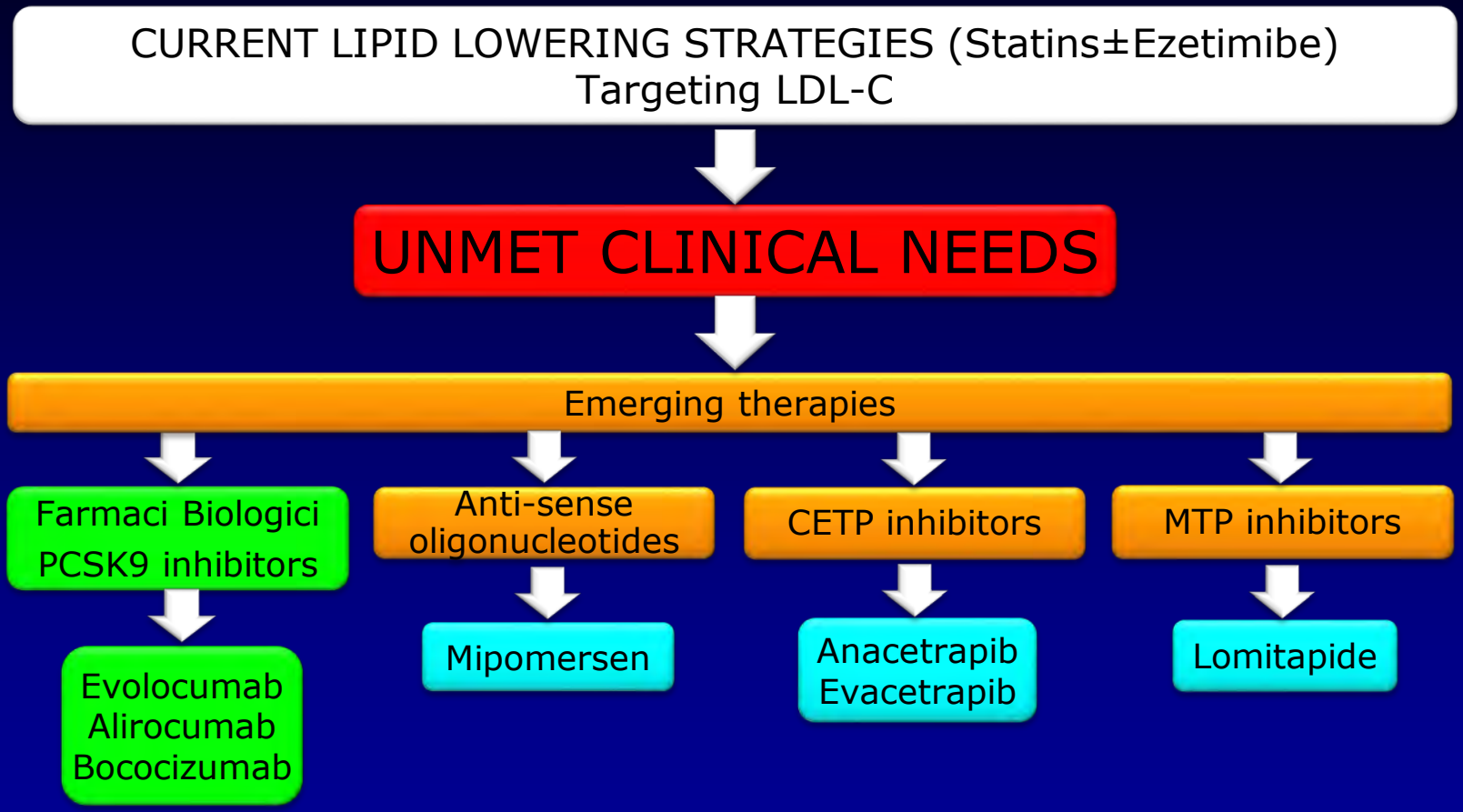
IMPROVE-IT: primary endpoint

(morte CV, angina, rivascolarizzazione, ictus)
simva 40 + eze 10 or placebo

la riduzione del LDL-C rimane la strategia di prevenzione CV più efficace, soprattutto nel diabete

Cannon CP et al.: NEJM, 372:2837, 2015

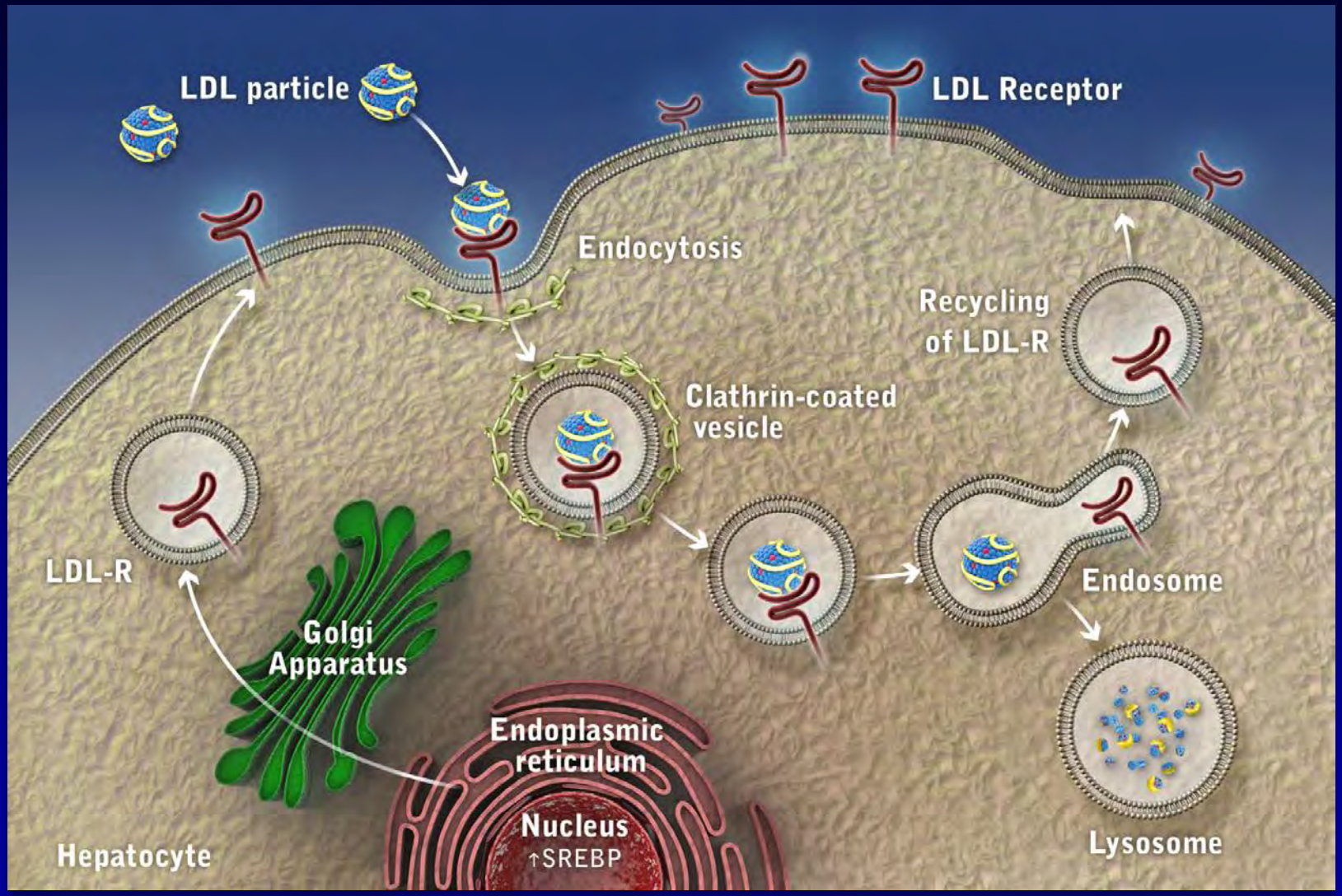
Emerging lipid-lowering therapies



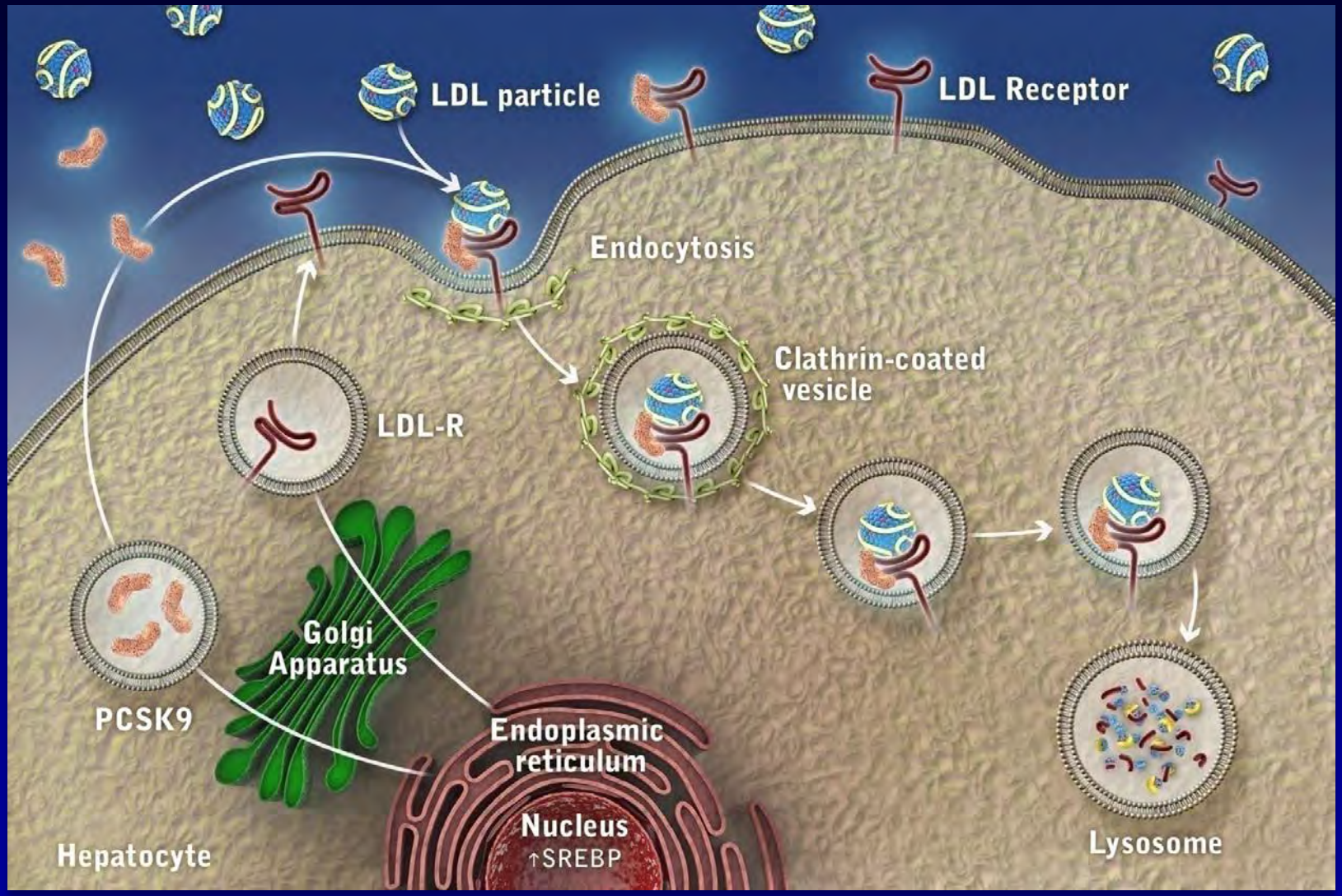
CETP, cholesteryl ester transfer protein; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; SI, statin intolerant

1. Sullivan D et al. J Am Coll Cardiol. 2012;308;2497–2508; 2. Stroes E et al. J Am Coll Cardiol. 2014;63;2541–2548; 3. Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects -3 (GAUSS-3), available at: http://clinicaltrials.gov/ct2/show/NCT01984424?term=NCT01984424%26rank=1, accessed October 2014; 4. Moriarty PM et al. Late-breaker abstract at AHA, Chicago, 15–19 November 2014; 5. ClinicalTrials.gov. The Evaluation Of PF-04950615 (RN316) In Reducing The Occurrence Of Major Cardiovascular Events In High Risk Subjects (SPIRE-2) available at: http://clinicaltrials.gov/ct2/show/NCT01975389?term=SPIRE-2andrank=1, accessed October 2014

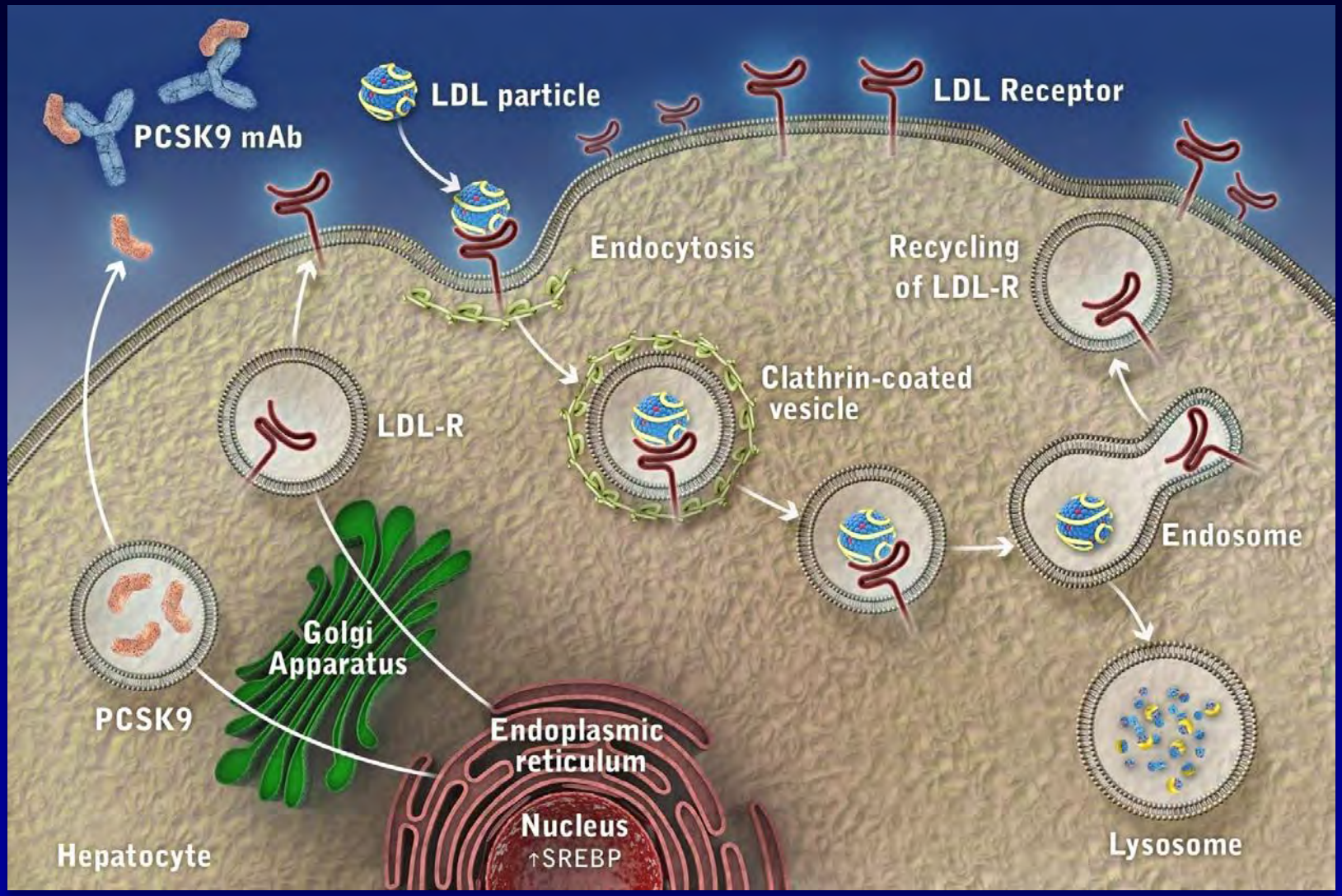
Funzione e Ciclo Biologico del Recettore LDL



Il Ruolo di PCSK9 nella Regolazione dell'Espressione del Recettore per le LDL



Impatto dell'Anticorpo contro PCSK9 sull'Espressione del Recettore delle LDL



PFIZER DISCONTINUES GLOBAL DEVELOPMENT OF BOCOCIZUMAB, ITS INVESTIGATIONAL PCSK9 INHIBITOR

Company will record a charge to GAAP and Adjusted earnings in the fourth quarter of 2016 estimated to be approximately $0.04 per share

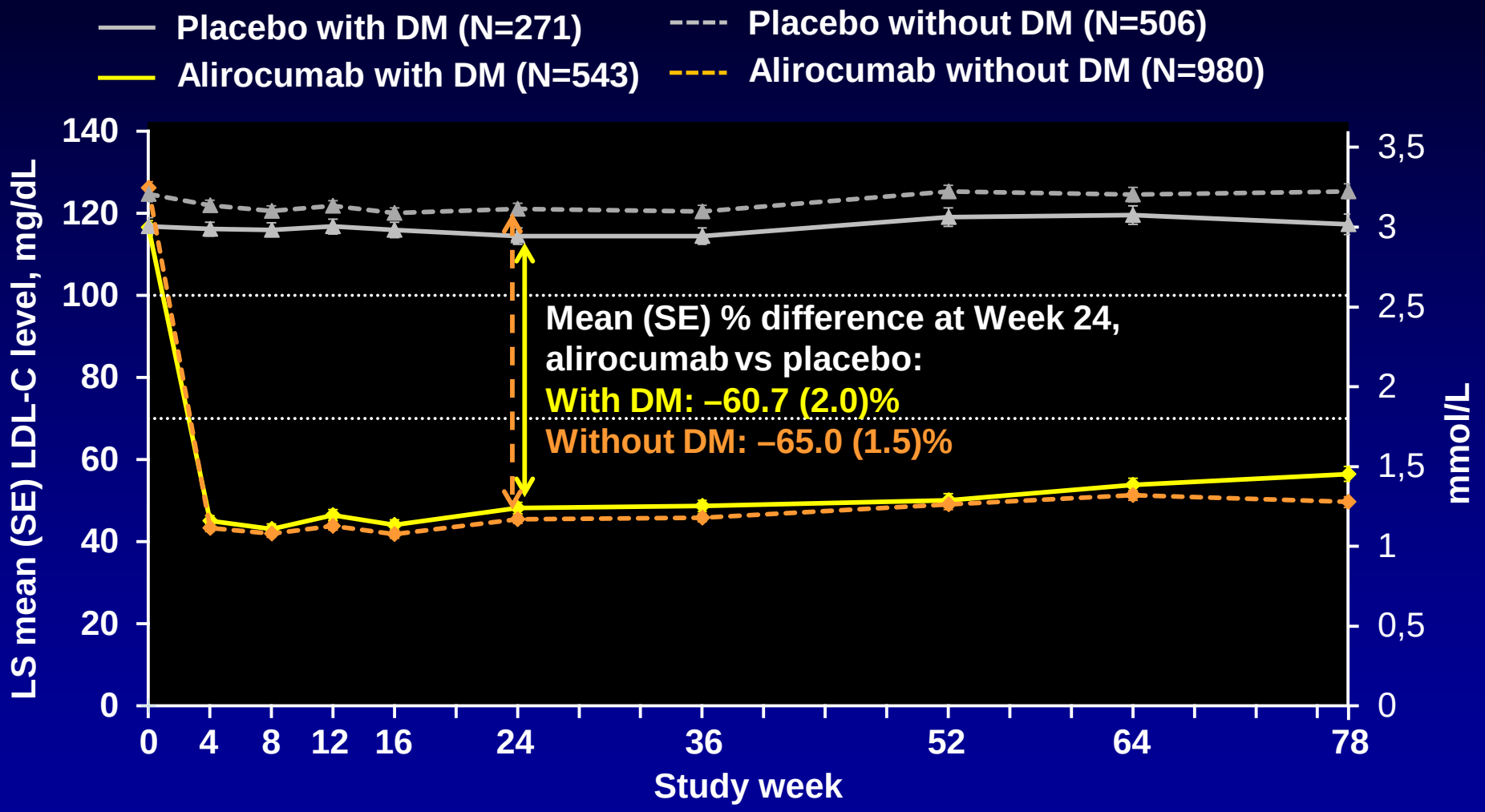
Tuesday, November 1, 2016 - 6:30am
EDT

Pfizer Inc. announced today the discontinuation of the global clinical development program for bococizumab, its investigational Proprotein Convertase Subtilisin Kexin type 9 inhibitor (PCSK9i). The totality of clinical information now available for bococizumab, taken together with the evolving treatment and market landscape for lipid-lowering agents, indicates that bococizumab is not likely to provide value to patients, physicians, or shareholders. As a result, Pfizer has decided to discontinue the development program, including the two ongoing cardiovascular outcome studies.

With the completion of six bococizumab lipid-lowering studies, Pfizer has observed an emerging clinical profile that includes an unanticipated attenuation of low-density lipoprotein cholesterol (LDL-C) lowering over time, as well as a higher level of immunogenicity and higher rate of injection-site reactions with bococizumab than shown with the other agents in this class. The goal of treating elevated cholesterol is to reduce the occurrence of cardiovascular events such as heart attacks and stroke, which requires long-term

LONG TERM Sub-analysis

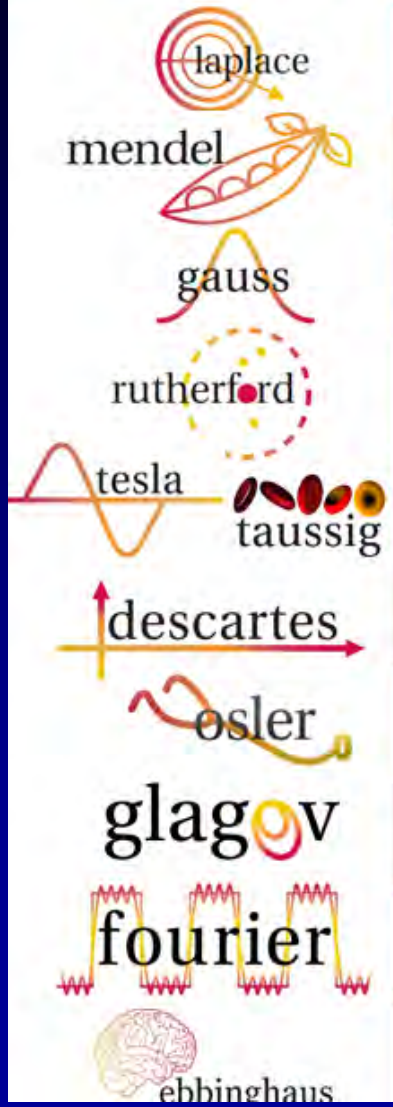
LDL-C Levels by DM Status (On-treat.)



Alirocumab 150mg Q2W

DM, diabetes mellitus. Colhoun HM et al. Oral #158 at EASD 2015, Stockholm, Sweden

Evolocumab: Programma PROFICIO



			>35,000 patients
Terapia di Associazione	Phase 2 (n=631)	Phase 3 (n=1896)
Monoterapia	Phase 2 (n=411)	Phase 3 (n=614)
Intolleranti a statine	Phase 2 (n=160)	Phase 3 (n=307) / Phase 3 (n=519)
Ipercolesterolemia Familiare Eterozigote	Phase 2 (n=168)	Phase 3 (n=329)
HoFH/ Severa FH	Phase 2/3 (n=58)	Phase 2/3 (n=300)
Sicurezza e efficacia a Lungo Termine		Phase 3 (n=901)
Estensione Open-label	Phase 2 (n=1324)	Phase 3 (n=4428)
Aterosclerosi		Phase 3 (n=950)
Prevenzione Secondaria		Phase 3 (n=27,564)
Neurocognition		Phase 3 (n=1972)

30% of patients with DM

Alirocumab: Programma ODYSSEY

14 TRIALS DI FASE 3 con >23 500 pazienti arruolati in >2000 centri internazionali

Ipercolesterolemici Familiari HeFH

In ASSOCIAZIONE a dose massima tollerata di statina (± altre LLT)

ODYSSEY FH I (NCT01623115; EFC12492) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=486; 18 months

ODYSSEY FH II (NCT01709500; CL1112) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=249; 18 months

ODYSSEY HIGH FH (NCT01617655; EFC12732) LDL-C ≥160 mg/dL n=107; 18 months

ODYSSEY OLE (NCT01954394; LTS 13463) Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717 n≥1000; 30 months

ODYSSEY LONG TERM (NCT01507831; LTS11717) LDL-C ≥70 mg/dL n=2341; 18 months

Ipercolesterolemia in pazienti ad alto rischio CV

In ASSOCIAZIONE a dose massima tollerata di statina (± altre LLT)

ODYSSEY COMBO I (NCT01644175; EFC11568) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=316; 12 months

†ODYSSEY COMBO II (NCT01644188; EFC11569) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=720; 24 months

ODYSSEY OUTCOMES (NCT01663402; EFC11570) LDL-C ≥70 mg/dL n=18 000; 64 months

Altre popolazioni

ODYSSEY MONO (NCT01644474; EFC11716) Patients on no background LLTs LDL-C ≥100 mg/dL n=103; 6 months

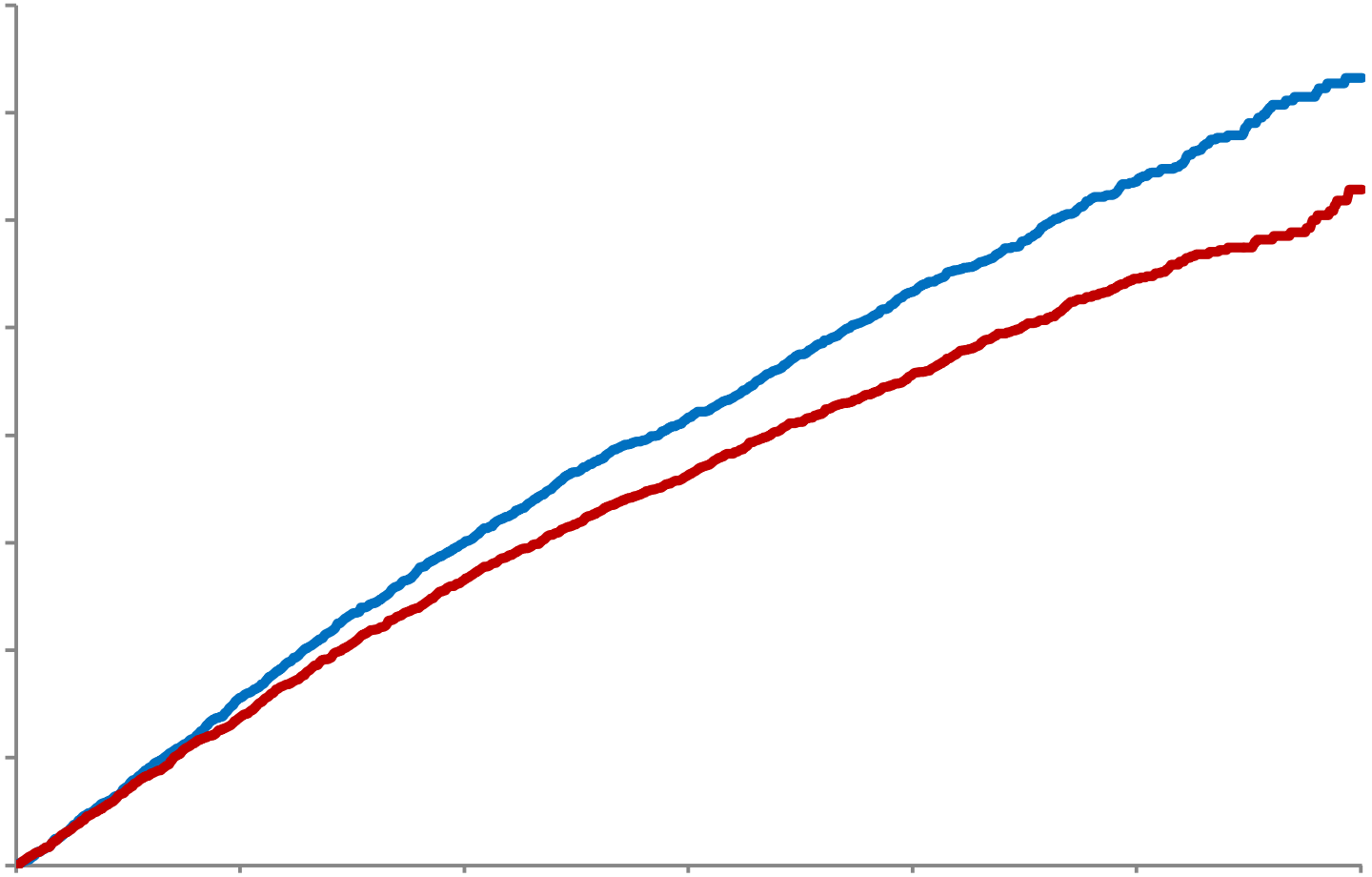
ODYSSEY ALTERNATIVE (NCT01709513; CL1119) Patients with defined statin intolerance LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=314; 6 months

ODYSSEY CHOICE I (NCT01926782; CL1308) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=700; 12 months

ODYSSEY CHOICE II (NCT02023879; EFC13786) Patients not treated with a statin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=200; 6 months

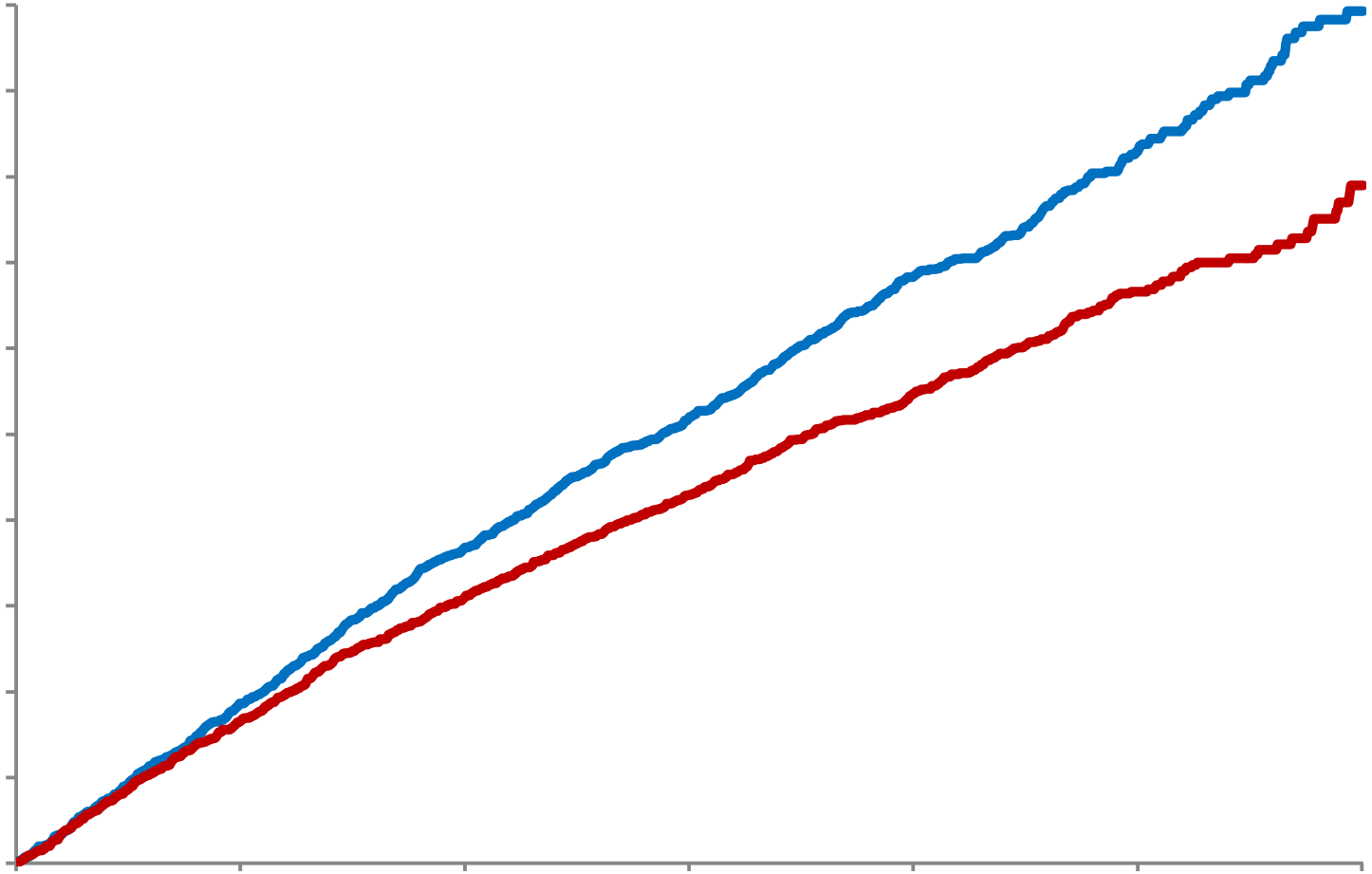
ODYSSEY OPTIONS I (NCT01730040; CL1110) Patients not at goal on moderate-dose atorvastatin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=355; 6 months

ODYSSEY OPTIONS II (NCT01730053; CL1118) Patients not at goal on moderate-dose rosuvastatin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=305; 6 months



The NEW ENGLAND JOURNAL of MEDICINE

Sabatine MS et al. NEJM 2017;376:1713



The NEW ENGLAND JOURNAL of MEDICINE

Sabatine MS et al. NEJM 2017;376:1713

ODYSSEY Diabetes Program

ODYSSEY DM-Insulin LPS14355
Alirocumab vs. placebo in patients with DM on insulin

ODYSSEY DM-Dyslipidemia LPS 14354
Alirocumab vs. usual care in patients with DM and mixed dyslipidemia

ADA 2017 Primary Results

EASD 2017 Full Results

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin
or,
alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin;
or
alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contra-indicated;

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies;

criteri AIFA

- Distanza dal Target
- On Top Massima Dose Tollerata STAT + EZT (>6 mesi)

PREVENZIONE PRIMARIA

Ipercolesterolemia Familiare Eterozigote
LDL-C ≥ 130 mg/dl

Trattamento **almeno 6 mesi** con **statine ad alta potenza** MTD + **ezetimibe**
oppure
Intolleranza alle Statine

PREVENZIONE SECONDARIA

Ipercolesterolemia Non Familiare
Dislipidemia Mista
LDL-C ≥ 100 mg/dl

Trattamento **almeno 6 mesi** con **statine ad alta potenza** MTD + **ezetimibe**
oppure
Intolleranza alle Statine

Ipercolesterolemia Familiare Eterozigote
LDL-C ≥ 100 mg/dl

Trattamento **almeno 6 mesi** con **statine ad alta potenza** MTD + **ezetimibe**
oppure
Intolleranza alle Statine

Ipercolesterolemia Familiare Eterozigote
Criteri per la Diagnosi del Dutch Lipid Clinic

		Punti
Storia familiare		
a) Parenti di primo grado con coronaropatia (CHD) prematura (<55 anni negli uomini; <60 anni nelle donne)		1
b) Parenti di primo grado con colesterolo >8 mmol/L (≥310 mg/dL) (o >95° percentile del Paese)		1
c) Parenti di primo grado con xantomi tendinei e/o arco corneale		2
d) Bambini <18 anni con colesterolo >6 mmol/L (≥230 mg/dL) (o >95° percentile del Paese)		2
Storia clinica		
a) Soggetto con CHD prematura (<55 anni negli uomini; <60 anni nelle donne)		2
b) Soggetto con malattia vascolare cerebrale o periferica prematura (<55 anni negli uomini; <60 anni nelle donne)		1
Esame fisico		
a) Xantoma tendineo		6
b) Arco corneale in un soggetto con <45 anni		4
Risultati biochimici (colesterolo LDL)	>8,5 mmol/L (>325 mg/dL)	8
	6,5-8,4 mmol/L (251-325 mg/dL)	5
	5,0-6,4 mmol/L (191-250 mg/dL)	3
	4,0-4,9 mmol/L (155-190 mg/dL)	1
Analisi del DNA		
a) Mutazione causative nota nei geni		8

Diagnosi "certa" con un punteggio >8 punti. Diagnosi "probabile" con un punteggio tra 6 e 8 punti. Diagnosi "possibile" con un punteggio tra 3 e 5 punti. Diagnosi "improbabile" con un punteggio tra 0 e 2 punti.

Consensus Statement of the EAS, European Heart Journal e-pub August 15, 2013

PDTA ipercolesterolemia familiare

1. Inquadramento della malattia
2. Strumenti per la diagnosi
3. Terapia
4. Controlli di salute
5. Modalità di accesso al Centro
6. Collaborazioni del Centro con altri centri nazionali ed internazionali

POLICLINICO UMBERTO I

Centro di Riferimento Regionale per la Diagnosi e Terapia dell'Ipercolesterolemia familiare
Medico responsabile: Dott. Marcello Arca - tel. 06 49974692 - marcello.arca@uniroma1.it
Viale del Policlinico, 155 - Roma (VII Padiglione, piano 1)

OSPEDALE PEDIATRICO BAMBINO GESÙ

Centro di Riferimento Regionale per la Diagnosi e Terapia dell'Ipercolesterolemia familiare
Medico responsabile: Dott. Andrea Bartuli - tel. 06 68593642 - andrea.bartuli@opbg.net
Piazza S. Onofrio, 4 - Roma (Padiglione S. Onofrio, piano 1)

FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI

Centro per le Malattie Endocrino e Metaboliche
Ambulatorio per le Dislipidemie
Medico responsabile: Prof. Andrea Giaccari - tel. 06 30158243-8244 - fax 06 94803782
colesterolo@policlinicogemelli.it
Largo Agostino Gemelli, 8 - Roma (3° piano ala A)

http://www.regione.lazio.it/malattierare/allegati/PDTA/RCG070_ipercolesterolemia_familiare.pdf

gli inibitori del PCSK9: quando usarli?

1. identificare i pazienti a rischio
   a. Dutch score (MyStar)
   b. genetica
   c. PDTA
2. stabilire il target
3. cercare con insistenza di raggiungerlo (secondo nota 13)
4. se ancora non a target, PCSK9i (secondo AIFA; Lazio?)

ricordarsi sempre che la riduzione del LDL-C è molto più efficace

caso clinico di ipercolesterolemia: xantelasma nell'incavo dell'occhio sinistro lipoma sulla mano

Ose L.: Curr Cardiol Rev. 4:60, 2008


Gian Pio
Francesca
Flavia
Ilaria
Teresa
Alice
Simona
Serena
Rachele

grazie Alice

gli inibitori del PCSK9: quando usarli?

1. target LDL
2. meccanismo PCSK-9
3. farmaci disponibili
4. pipeline trials
5. uscita Pfizer
6. primi trial di efficacia
7. effetti collaterali, sicurezza (incluso diabete) iniettivo, emivita, dosaggi
8. primo trial su CVD
9. trial in arrivo
10. trial specifici per diabete
11. indicazioni EMA
12. rimborsabilità AIFA
13. dutch score (importanza genetica)
14. PDTA Lazio
15. frequenza forme omozigotiche (solo evolocumab)
16. dislipidemia mista nel diabete (non efficacia su trigliceridi)
17. costi, centri prescrivibilità
18. quando usarli: a tutti quelli in cui è possibile prescriverli